REMARKS

Claim 9 has been amended to correct typographical errors. Claims 1-10 remain pending after entry of this Amendment.

Objections to the Drawings:

The drawings have been objected to under 37 CFR 1.121(d) as the references numbers have been manually written with respect to FIGS. 4 and 6-7.

Applicants are in the process of preparing formal drawings and will submit the formal drawings as soon as they are available.

Claim Rejections under 35 U.S.C. § 102(b)

Claims 1-8 stand rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by U.S. Patent No. 5,567,294 ("Dovichi *et al.*"). Claims 9-10 stand rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by U.S. Patent No. 5,194,921("Tambo *et al.*"). Applicants traverse the rejection.

It is established that a claim is anticipated under 35 U.S.C. § 102 only if each and every limitation as set forth in the claim is found, either expressly or inherently described in a single prior art reference. Neither Dovichi *et al.* nor Tambo *et al.* teach each and every limitation recited in instant Claims 1-8 and/or 9-10.

Dovichi *et al.* teach a multiple capillary biochemical analyzer for sequencing DNA and performing other analyses, in which a set of capillaries extends from wells in a microtiter plate into a cuvette. As shown in FIGS. 1-2, a laser 130 or other source of collimated electromagnetic radiation provides a collimated beam 132 of light that is aligned to pass from a focusing lens 134 into the chamber 34, as close as possible above the barrier member 90. Alternatively, the beam 132 may be split into a set of parallel beams with appropriate optics, with one parallel beam per row of capillaries.

Fluorescence is excited in the chamber 34, above the barrier member 90. The fluorescence passes through the holes 80 in barrier member 90, through the glass window 100 at the bottom of lower chamber 102, and through a two element air-spaced condenser lens 136, typically operated at unit magnification. The condenser 136 images the fluorescence onto a photodetector 138. A spectral filter shown diagrammatically in dotted lines at 139 may be used to isolate fluorescence from specific dyes. See also Col. 5, lines 29-46.

Instant Claim 1 calls for a multicolor particle analyzer including a capillary, means for projecting a light beam through said capillary to illuminate a predetermined volume in said capillary, means for causing a sample containing sample particles which naturally fluoresce or are tagged to fluoresce and emit light at one or more distinct wavelengths to flow along the capillary through said predetermined volume, a tunable filter for receiving said light emitted by each particle and repetitively passing light pulses for each wavelength of light emitted by each particle as it passes through said predetermined volume, and a detector for detecting the output light from said tunable filter and providing an output pulse for each light pulse at each of said multiple wavelengths.

Instant Claim 4 calls for a multicolor particle analyzer for analyzing particles each of which emits light at multiple distinct wavelengths as they pass through an analyzing volume comprising a tunable filter for receiving the emitted light and repetitively passing light at said distinct wavelength as said particles pass through the analyzing volume; and a single detector for receiving the light from the tunable filter and providing output signals for each distinct wavelength as the particle passes through the analyzing volume.

Instant Claim 5 calls for a method of analyzing particles each of which fluoresces and emits light at multiple different distinct wavelengths responsive to excitation light which comprises the steps of causing the particles to flow through an analyzing region; applying excitation light to the analyzing region to cause each particle to emit light at its distinctive wavelengths as it passes through the analyzing region; receiving the emitted

light with a tunable optical filter to repetitively and sequentially pass light at each of said multiple distinct wavelengths; and detecting the light passed by the filter with a single detector to provide output signals representative of the distinct wavelengths.

Instant Claim 7 calls for a particle analyzer for analyzing particles in a sample fluid which fluoresce and emit light at one or more wavelengths. The particle analyzer comprises a capillary for receiving the sample fluid, a pump for causing the sample fluid to flow through the capillary, a light source for projecting a light beam through the capillary to illuminate a predetermined region along the capillary whereby singulated particles flow through the illuminated region and emit fluorescent light at the one or more wavelengths, a tunable optical filter responsive to tuning pulses for receiving the florescent light and repetitively passing pulses of light at said one or more wavelengths as a particle passes through said region, a detector for receiving said light pulses and provide an output signal for each of said pulses, and, a processor configured to receive said out signals and provide an output signal representative of the amplitude of each of said one or more fluorescent wavelengths.

Instant Claim 9 calls for a method of analyzing particles in a fluid which fluoresce at one or more wavelengths comprising the steps of causing the fluid to flow past a source of illumination whereby particles emit fluorescent light at the one or more wavelengths; periodically detecting the emitted characteristic fluorescence of said particles as the particles flow through the illumination source; and providing output signals representative of the characteristic wavelength of each of said particles.

Dovichi *et al.* do not teach or suggest means or a light source for projecting a light beam through said capillary to illuminate a predetermined volume in said capillary as called for by instant Claim 1 or 7. Dovichi *et al.* teach that at the ends 24 of the capillary tubes 26, the sheath fluid entrains sample fluid from the capillaries, in the form of individual filaments 126 of fluid, as best shown in FIG. 11. See also Col. 5, lines 20-23. A laser 130 provides a collimated beam 132 of light that is aligned to pass from a focusing lens 134 into the chamber 34, as close as possible above the barrier member

90. See Col. 5, lines 29-32. The collimated beam 132 illuminates the sheath fluid and filament 126 as shown in FIG. 11. Dovichi *et al.* do not teach projecting a light beam through the capillary to illuminate a predefined volume in the capillary. Indeed, Dovichi *et al.* teach a sheath flow particle analyze, but do not teach or suggest a capillary particle analyzer as recited in instant Claim 1, 4 or 7.

Nor do Dovichi *et al.* teach or suggest a tunable filter for receiving light emitted by each particle and repetitively passing light pulses for each wavelength of light emitted by each particle as it passes through the predetermined volume, as called for by instant Claim 1, or a tunable filter for receiving the emitted light and repetitively passing light at said distinct wavelength as said particles pass through the analyzing volume as called for by instant Claim 4, or a step of receiving the emitted light with a tunable optical filter to repetitively and sequentially pass light at each of said multiple distinct wavelengths as called for by instant Claim 5, or a tunable optical filter responsive to tuning pulses for receiving the florescent light and repetitively passing pulses of light at one or more wavelengths as a particle passes through the predetermined region, as called for by instant Claim 7, or a step of periodically detecting the emitted characteristic fluorescence of said particles as the particles flow through the illumination source as called for by instant Claim 9. Relying on Col. 5, lines 1-55, the Examiner argued that Dovichi *et al.* has taught a tunable filter for receiving light emitted by each particle and repetitively passing light pulses for each wavelength of light emitted by each particle as it passes through the predetermined volume. However, in the relevant text at Col. 5, lines 44-45, Dovichi *et al.* only teach that the filter 139 can be a tunable filter, or a set of filters on a rotating wheel, or can be a grating or a prism. Dovichi *et al.* do not teach a tunable filter that repetitively passes light pulses for each wavelength of light emitted by each particle as it passes through the predetermined volume.

The Examiner is respectfully referred to the Specification where an example of the tunable filter called for by the instant claims is provided. In the paragraph beginning at page 5, line 7, it is described that:

> Referring particularly to Figure 2, as a particle passes through the detection volume 16 the fluorescence is periodically detected when the wavelength pass band corresponds to the fluorescent wavelength of the particle. Assume the laser beam 14 has thickness of 20 μm and the capillary dimensions a = b = 0.1mm, and the volume of sample from the inlet 26 to the detection volume is 200 nanoliters and the probe volume is .2 nanoliters. Assume further that the flow rate is 1 microliter per second, then the particle velocity is 100mm/s and the transit time through the detection volume is 200 μs. Assume that the acousto-optic filter can shift its pass band in 10 microseconds or less, this would result in sampling the fluorescent emission of each particle in a four color system about 5 times. It is apparent that if the acousto-optic filter can shift at a greater frequency, more samples can be taken or, in the alternative, a larger number of fluorescence colors can be detected and provide sufficient sampling points to reconstruct the fluorescence trace. It is also to be of particular note that the system requires small volumes of sample. The system is ideally suited for cell subset analysis wherein only small volumes of blood are available. This permits cell analysis which were, heretofore, difficult to perform because of the small volume of blood available, for example from infants, small animal species, mice, rats and other living organisms. The ability to analyze small volumes of blood from a living organism will allow characterization of blood cell populations without sacrificing the animals and will permit longitudinal studies where samples can be taken from a single animal at periodic intervals.

Therefore, the tunable filter or acousto-optic filter called for by the instant claims shifts its pass band for example in microseconds or less during detection, which results in sampling the fluorescent emission of each particle in a multiple color system multiple times as particles pass through the detection volume. The filter's pass band is shifted so that one or more emission wavelengths are scanned multiple times during the period that it takes for a particle to pass through the detection volume. As described in the above example, the transit time of a particle through the detection volume is 200 microseconds and the time required for the acousto-optic filter to scan through four different colors is 40 microseconds (10 microseconds each time the transmission band of the filter is shifted to a new color). As a result, it is possible to sample each color 5 times while the particle is flowing through the detection volume. Multiple samples are advantageous in that they allow noise reduction through signal averaging.

Dovichi *et al.* do not teach or suggest the tunable filter as called for by Claim 1, 4, 5, 7, or 9. Dovichi *et al.* teach a filter that has a fixed pass band during detection. A set of filters on a rotating wheel, or a grating or a prism used in Dovichi *et al.* as taught at Col. 5, lines 47-48 precludes use of a tunable filter for repetitively passing light pulses for each wavelength of light emitted by each particle as it passes through the predetermined volume.

Moreover, the system taught in Dovichi *et al.* detects a single color during the transit time of the particle. Dovichi *et al.* do not teach detecting more than one color during the transit time as called for by instant Claim 4 or 5.

Claims 2-3, 6, 8 and 10 depend on Claim 1, 5, 7, and 9 respectively and recite further limitations. They are therefore allowable for at least the same reasons as for Claims 1, 4, 5, 7, and 9 and for reasons of addition limitations recited therein.

Claims 2 and 8 are further allowable as they call for an acousto-optic filter. Dovichi *et al.* do not teach or suggest an acousto-optic filter at Col. 5, lines 44-48.

Claim 3 is further allowable as it calls for a detector for detecting light scattered by the particles as they travel through the predetermined volume. Dovichi *et al.* do not teach or suggest a detector for detecting light scattered at Col. 5, lines 23-45. Dovichi *et al.* teach a method for static viewing of fluorescent emission along the flow direction.

Claim 7 is further allowable as it calls for a pump for causing the sample fluid to flow through the capillary. Dovichi *et al.* teach a sheath fluid source 110 in Col. 4, lines 65-67. In Dovichi *et al.*, a high voltage source 120 provides a driving voltage of *e.g.* 30 kV which, via the fluid in chamber 34, appears across the length of the capillaries 26. The electric field created by the voltage source 120 causes fragments of sample DNA from the wells 30 to migrate through the matrix or gel in the capillaries 26. At the ends 24 of the capillary tubes 26, the sheath fluid entrains sample fluid from the capillaries, in the form of individual filaments 126 of fluid, as shown in FIG. 11. Dovichi *et al.* do not

teach or suggest a pump for causing the sample fluid to flow through the capillary as called for by Claim 7.

Tambo *et al.* teach a method and an apparatus for detecting the status of a flocculation process of components in a liquid. Tambo *et al.* use a beam of light including at least two wavelengths λ_1 and λ_2 which exhibit distinct or dominant absorption or scattering characteristics with regard to a suspended component and a flocculated component in a sample liquid. The beam of light irradiates the sample which includes a plurality of components to be flocculated. Then, the transmitted or absorbed amount of the wavelength components of λ_1 and λ_2 through the sample liquid are simultaneously measured so that a correlation coefficient between the two wavelength components of the transmitted beam is calculated in real time, thereby measuring the progress of the flocculation process. See Col. 6, lines 21-33. As shown in FIG. 1, an illumination beam of light 2 emitted from a xenon lamp 1 is condensed by a reflector 3, is incident to a collimator 4, is further shaped by a slit 5 into a beam having a predetermined cross-sectional shape, and is incident onto a sampling liquid 7 flowing in the direction indicated by an arrow P in a flow cell 6 made of fused quartz. A beam of light 8 transmitted through the sampling liquid 7 is passed through a slit 9 identical to slit 5, and is incident to a half mirror 10. The half mirror 10 splits the beam into two beams: one of the two beams is incident to a photodiode 13 through an interference filter 11; and the other beam is incident to a photodiode 14 through an interference filter 12. The photodiodes 13 and 14 produce voltage signals V_1 and V_2 across load resistors 15 and 16, respectively. See FIG. 1 and Col. 8, lines 18-34.

Instant Claim 9 calls for a method of analyzing particles in a fluid which fluoresce at one or more wavelengths. The method comprises the steps of causing the fluid to flow past a source of illumination whereby particles emit fluorescent light at the one or more wavelengths, periodically detecting the emitted characteristic fluorescence of said particles as the particle flow through the illumination source, and providing output signals representative of the characteristic wavelength of each of said particles.

Tambo *et al.* do not teach or suggest a multicolor analyzer for analyzer particles each of which emits light at multiple distinct wavelengths as they pass through an analyzing volume. To the contrary, Tambo *et al.* teach an apparatus that uses two wavelengths λ_1 and λ_2 which exhibit distinct or dominant absorption with regard to a suspended component and a flocculated component in a sample liquid. Nor do Tambo *et al.* teach or suggest a tunable filter for receiving the emitted light and repetitively passing light at the distinct wavelength as the particles pass through the analyzing volume. To the contrary, Tambo *et al.* teach two interference filters 11 and 12 which have fixed frequency. The interference filters taught by Tambo *et al.* are not tunable filters.

Claim 10 depends on Claim 9 and recites further limitations. Claim 10 is therefore allowable for at least the same reasons as for Claim 9 and for reasons of additional limitations recited therein.

Based on the foregoing reasons, Applicants respectfully request reconsideration of the rejections of Claims 1-10 under 35 U.S.C. 102 over Dovichi *et al.* and Tambo et al.

Applicants respectfully submit that the instant application is in condition for allowance. An early indication of the same is therefore respectfully requested. If any matters can be resolved by telephone, the Examiner is invited to call the undersigned attorney at the telephone number listed below.

No fees beyond those being submitted concurrently herewith are believed due. The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-

0872. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 50-0872.

Respectfully submitted,

Date December 18, 2006

By _____

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